

Bladder Cancer: Chemoprevention, Surveillance

Steven C. Campbell, MD, PhD
Section of Urological Oncology
Glickman Urological Institute



Cleveland Clinic

Improving Outcomes for Patients with Bladder Cancer

- Restaging TURBT
- Chemotherapy in RR
- Timely referral for R Cx
- Adherence to surgical standards for R Cx: Quality of surgery matters!
- Rational use of chemotherapy
- All applied in suboptimal manner in USA!!!

Improving Outcomes for TCC

- Prevention: Smoking cessation and chemoprevention
- Surveillance: rational approaches

Prevention: Rationale Strong for Environmentally Caused Cancer

- Smoking cessation
- Increase hydration: dilutes carcinogens
- Consume less dietary fat: less oxidative damage
- Chemoprevention

See you in the Cysto Suite



Chemoprevention in Urology

- **PCPT**: Proscar reduced incidence of CAP
- **SELECT**: Selenium and Vit E – over 35,000 enrolled, matured in 2008
- **TCC**: most actively studied, only few positive studies

Chemoprevention for Bladder Cancer Rationale

- **Multistep process** (several targets): can block tumor initiation, promotion, factors that promote progression, or enhance host defenses
- **Chronic recurrent course**
- **Easily recognized lesions**
- **Well defined populations at risk: particularly those with hx TCC**

Hedgepeth, Jones, Campbell, Up-to-Date, 2007

Vitamins

Vitamin	Mechanism	Results	Consensus
Retinoids Vitamin A & analogues	Promotes differentiation Antioxidant	Conflicting studies	Side effects a major concern in this setting
Pyroxidine (B6)	Breaks down tryptophan metabolites	Conflicting studies	Not promising
Vitamin C	Antioxidant	Conflicting studies	Concern about potentiation of cancer
Vitamin E	Antioxidant	Conflicting studies	Further study indicated

Retinoids (Vit A and analogues)

- In vitro: positive effects
- Human epidemiologic studies conflicting
- Animal studies suggest benefit
- ATBC trial (smokers): no correlation between bladder Ca incidence and dietary levels of retinol or beta-carotene
- Eretinate study: suggested benefit but 3 MI's in study group
- Feretinide study: No effect on recurrence at one year

Megadose Multivitamins

Lamm et al, 2004

- N = 65
- Randomized to RDA of multivitamins vs. Megadose (? A, B6, C, and E)
- No difference in recurrence in 1st year
- At 5 yrs: 80% recurrence in RDA and 40% in Megadose groups
- Small study, would benefit from larger, independent study

Dietary Micronutrients

	Mechanism	Results	Consensus
Selenium	Antioxidant Immune enhancing	Conflicting studies	Warrants further study
Isoflavones	Growth inhibition, induction apoptosis	? Soy intake correlated with ? incidence TCC	Lab data promising, consider further study
Green Tea Polyphenols	Antioxidants	Epidem study suggests benefit	Prospective study underway

Synthetic Compounds

Compound	Mechanism	Result	Consensus
DMFO	Inhibits polyamine synthesis	No benefit	Not promising
NSAID/Cox 2 inhibitors	Inhibit PG synthesis	Epidem studies suggest benefit Concern over cardiac effects	Prospective trial in progress
Oltipraz	Detoxifies carcinogens	Rodent studies promising	Further study needed
EGFR inhibitors	Blocks growth factors	Minimal data available for TCC	Phase II trial underway

Take Home Message Chemoprevention

- Only few studies positive
- Promising agents for future study
 - Vit E, green tea polyphenols, NSAIDs, oltipraz, EGFR inhibitors
- Consider Oncovite: 2 per day

Improving Outcomes for TCC

- Prevention: Smoking cessation and chemoprevention
- Surveillance: rational approaches

Surveillance Costs

- Urologic cancers: 22% of all cancers
- Cost of surveillance exorbitant
- Typical visit
 - Lab: \$1-200
 - CXR and CT: \$2000
 - 99213: 0.67 RVU = \$50
- Total for 5 years = ~~\$20,000~~



~~Cancer
Survivor~~

**Surveillance
Survivor**

Cost of Surveillance

- Bladder CA
 - Costs each year twice that of CAP
 - Largely due to surveillance
 - Endoscopic
 - Upper tracts
 - Diversion related

**Agency for Health Care Policy and Research,
US Public Health Service, 1999**

Surveillance: Factors to Consider

- Where do recurrences develop?
- When?
- How do they present: symptomatic or not?
- What patients are at highest risk?

What Tests are Useful?

- Sensitivity, specificity
- Costs, direct and indirect (due to false positives)
- Inherent risks
- Can it detect asymptomatic recurrences?

Which Recurrences are Potentially Salvageable?

- RCC: Lung: more indolent, potentially salvaged
- Testis CA: most recurrences salvageable
- Bladder cancer: Urothelial most likely and usually salvageable

BCA: Randomized Trials

Natl. Research Council on BCA Follow-up

- Routine vs. Intensive follow-up (added BS, CXR and blood tests): N =1243
- No difference in overall survival
- Intensive follow-up
 - Shortens disease free interval
 - Exposes more patients to treatment related side effects

ASCO Guidelines: BCA

- Hx, PE
- Monthly self exam, yearly mammogram
- Educate about signs of recurrence
- CMP, tumor markers
- ~~CXR, BS, CT~~

Smith, et al., J Clin Onc, 17:1080, 1999

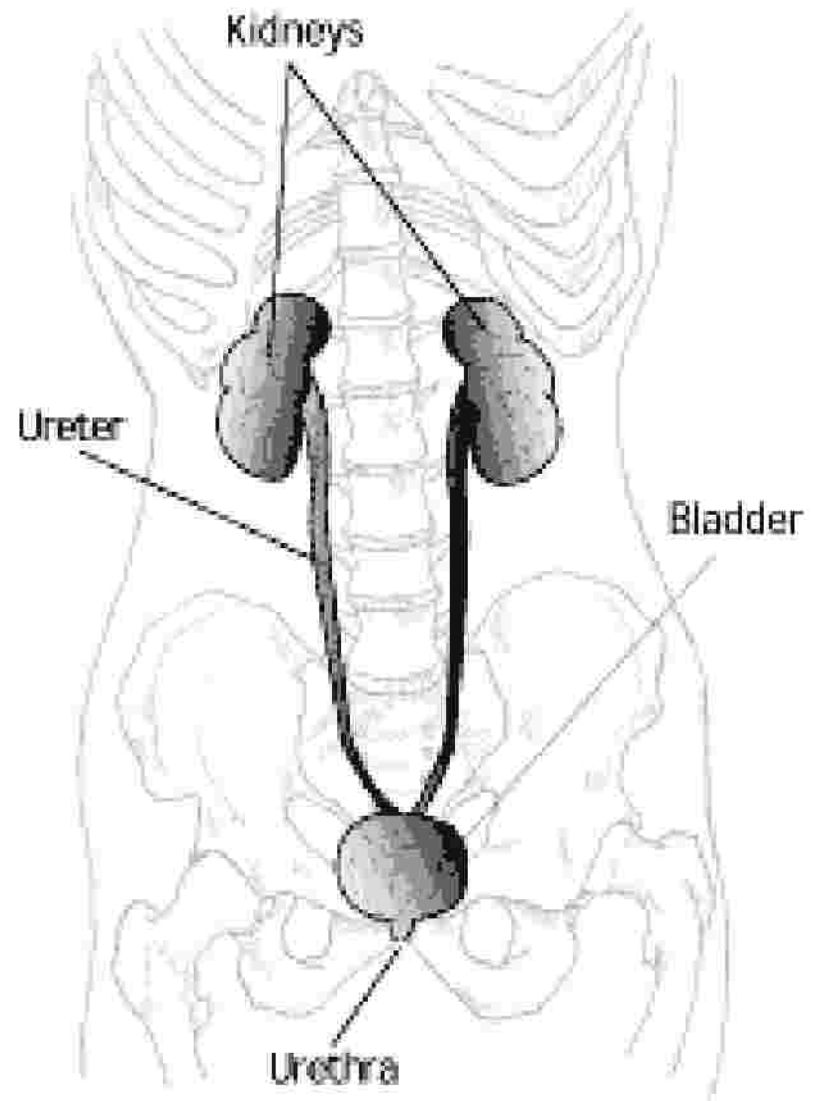
Colon CA

Patient Perceptions

Question	Not at all	Rather or very much
Nervous prior to visit?	51%	21%
Reassured after visit?	4%	80%



Surveillance for Bladder Cancer



Surveillance Cysto/Cytol

- Q 3 mo for 2 yrs
 - Q 6 mo for 2 yrs
 - Annual thereafter

 - High risk: as above
 - Low risk: can attenuate
- Risk factors:
 - pT1, high grade, associated CIS
 - Multifocality, tumor size > 3 cm
 - Recurrence at 3 months
 - Hx prior intravesical Rx, pattern recurrence

Donat, UCNA, 30:765, 2003

LGLS Bladder Cancer

Oosterlinck, et al, Urology, 2005

- ? to higher grade: 11-17%
- ? to = T2 : 2-4%
- Soloway observed for mean 38 mo: 3/32 (9.4%) ? to higher grade or stage
- If solitary or limited: cysto at 3 mo, 12 mo, then yearly, then stop at 5 yrs



Role of Molecular Markers

- BTA stat, NMP22, Telomerase, etc
 - Good sensitivity for LG disease
 - Not as specific as cytology
- **Ultimate role not defined:** Might allow reduction in frequency of cystoscopy

Glas, et al., J Urol, 169:1975, 2003

FISH (UroVysion)

- Sensitivity 69-87%
- Specificity: 89-96%
- FISH at end of intraves. Rx may predict outcomes
- **Anticipatory positives:** 15/36, mean of 6.0 months
- Effect on survival? Similar to ultrasensitive PSA?

Sarosdy, et al., J Urol, 168:1950, 2002

Lokeshwar et al, Urology, 66, Suppl 6A: 35-63, 2005

Kipp et al, J Urol, 173:401-4, 2005

Upper Tracts

- High risk: 15% at 5 years, 25% at 10 years, 33% at 15 years
- Yearly IVP or CT urogram
- Low risk: 2-3% overall
- No evidence that radiographic detection imparts advantage
- Surveillance can be attenuated

Herr, J Clin Onc, 16:1099, 1998

UT Recurrence: Ta Bladder Ca

- Overall: 3.4% rec. rate
- Multifoc. and rec. within 12 mo: 4.5X ? risk
- All others: UT rec. rare ? UT imaging not required

Canales et al, J Urol, 175:74-77, 2006
Jewett M, J Urol, 175:12-13, 2006



IVP with papillary tumor of the renal pelvis Intravenous pyelogram (IVP) demonstrating filling defects in the renal pelvis (arrows), characteristic of papillary tumor. Courtesy of Machele Donat, MD

Radical Cystectomy

- N = 382 patients, 97 with recurrence
- 74% asymptomatic: CXR and labs had highest yield
- Surveillance CT:
 - Asymptomatic, isolated recurrence detected in 10 patients, 9 had T3 disease

Slaton, et al., J Urol, 162:710, 1999

SP Radical Cystectomy

Stage	Routine Surveillance
pT1N0	Hx, PE, CBC, CMP, CXR, cytol q yr IVP q yr x2, then every other year No CT's
pT2N0	Same, except q 6 mo for 3 yrs, then annually No CT's
pT3N0	Same, except add CT at 6, 12, and 24 months

SP Rad Cx

- Other issues
 - Diversion related
 - Acidosis, B12, vitamin A/D levels after 1st few years
 - Hydronephrosis, stones, pyelonephritis
 - Parastomal hernia
 - Urethral recurrences

